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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/44, 31/415</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/16228</b> <b>(43) International Publication Date:</b> 23 April 1998 (23.04.98)
<b>(21) International Application Number:</b> PCT/SE97/01651 <b>(22) International Filing Date:</b> 1 October 1997 (01.10.97) <b>(30) Priority Data:</b> 9603725-4      11 October 1996 (11.10.96)      SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LINDBERG, Per [SE/SE]; Gundas Gata 40, S-431 51 Mölndal (SE). PINAS-MASSO, Joan [ES/ES]; 2 <sup>a</sup> -3 <sup>o</sup> piso, Placa Francesc Masia, 8, E-08029 Barcelona (ES). SERRA-CARRERAS, Jordi [ES/ES]; 1 <sup>o</sup> -3 <sup>o</sup> piso, Paseo Pere III, 71ü, E-08240 Manresa (ES). TRO- FAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
<b>(54) Title:</b> USE OF AN H <sup>+</sup> , K <sup>+</sup> -ATPase INHIBITOR IN THE TREATMENT OF NASAL POLYPS <b>(57) Abstract</b> <p>The invention provides a method for the treatment of polyposis which comprises treating a subject suffering from polyposis with an H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor and, optionally, a glucocorticoid. The invention also relates to a pharmaceutical formulation for simultaneous, separate or sequential administration in the treatment of Widal's Syndrome and in the treatment of asthma.</p>		

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USE OF AN  $H^+$ ,  $K^+$ -ATPASE INHIBITOR IN THE TREATMENT OF NASAL POLYPS*Field of the invention*

The present invention provides a new treatment for polyposis using proton pump inhibitors (PPIs), i.e.  $H^+$ ,  $K^+$ -ATPase inhibitors.

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*Background of the invention*

Polyposis can generally arise in the nose and the gastrointestinal tract. In the nose, polyps are pale bags of tissue that arise in the nasal cavity. Their paleness is generally due to poor blood supply. It is not known what causes the polyps to be formed but their presence is often associated with certain medical conditions, for example asthma and aspirin  
10 intolerance. Within the general population the incidence of nasal polyps is low at around only 1% but 13% of asthma sufferers and 36% of aspirin intolerant asthmatics suffer from nasal polyposis. The triple condition of nasal polyposis, aspirin intolerance and asthma is known as Widal's Syndrome.

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Nasal polyposis is generally treated in two stages. Initially a reduction in size of the polyps is achieved either by surgery or by the application of a topical intranasal steroid preparation, for example betamethasone sodium phosphate. Once a reduction in size has been obtained then long term maintenance of the reduction is necessary by regular use of  
20 an intranasal steroid spray such as beclomethasone dipropionate, budesonide, or fluticasone propionate. When rapid amelioration is required, oral steroids such as prednisolone or dexamethasone or synthetic adrenocorticotrophic hormones are used (see V J Lund Diagnosis and treatment of nasal polyps Brit Med J 1995, 311, 1411-4). There are also proposals that non-steroidal antiinflammatory drug can be used in the treatment of nasal  
25 polyposis (see WO 9703659-A).

*Detailed Description of the Invention*

According to the invention there is provided a method for the treatment of nasal polyps which method comprises treating a subject suffering from the said condition with an  $H^+$ ,

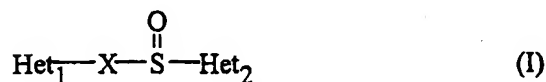
K<sup>+</sup>-ATPase inhibitor. The invention further provides the use of an H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor in the manufacture of a medicament for the treatment of nasal polyps.

H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are a known class of pharmaceutical agents generally used in therapy for the treatment of gastric acid related diseases. Examples of H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Some of these compounds are for instance disclosed in EP-A1-0005129, EP-A1-174726, EP-A1-166287 and GB 2163747.

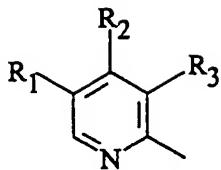
These pharmaceutical substances are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers.

It has now surprisingly been found that H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are useful in the treatment of nasal polyps, particularly where known treatments have failed.

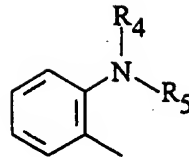
The H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors preferably used in the invention are compounds of the general formula



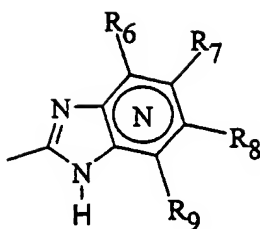
wherein Het<sub>1</sub> is



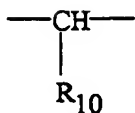
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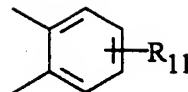
Het<sub>2</sub> is



and X is



or



wherein N in the benzimidazole moiety of Het<sub>2</sub> means that one of the ring carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub> and R<sub>3</sub> each independently represent hydrogen, alkyl, or alkoxy on the condition that R<sub>1</sub> and R<sub>3</sub> do not simultaneously represent alkoxy; and R<sub>2</sub> represents alkyl, alkoxy optionally substituted by fluorine, alkylthio or alkoxyalkoxy; or one of R<sub>1</sub> and R<sub>3</sub> is halogen and the other is hydrogen and R<sub>2</sub> is 1-morpholino, 1-piperidino or dialkylamino;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen and alkyl;

$R_6$ - $R_9$  are the same or different and selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy, alkylcarbonyl, and alkoxycarbonyl;

- 5  $R_{10}$  is hydrogen or  $R_{10}$  and  $R_3$  together complete a ring containing 6 to 8 carbon atoms;  
and

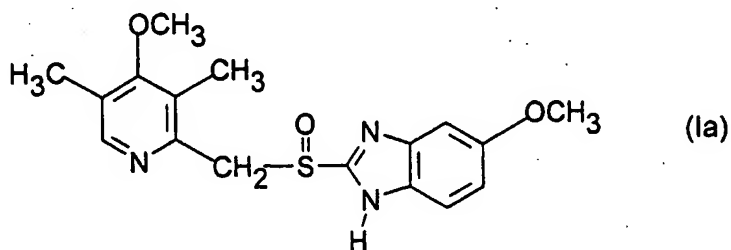
$R_{11}$  represents hydrogen, halogen or alkyl;

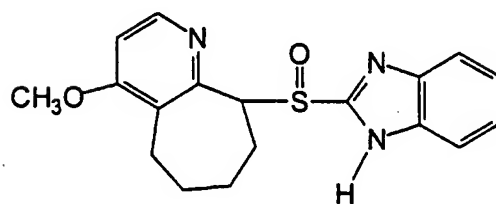
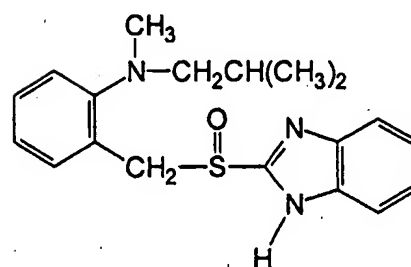
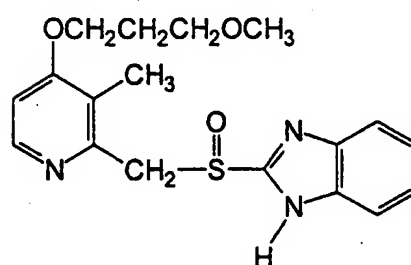
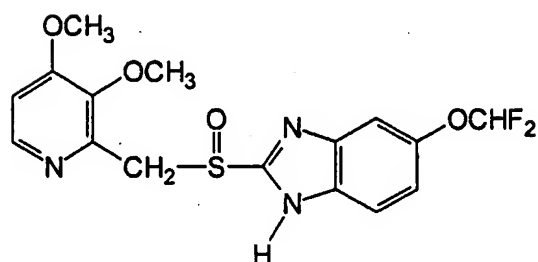
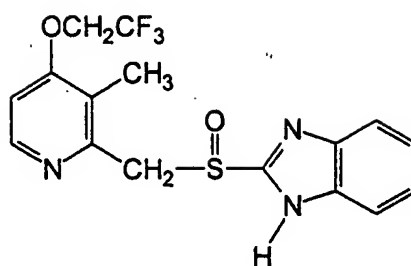
- 10 wherein the compound of formula (I) is optionally in the form of a pharmaceutically acceptable alkaline salt or in its neutral form or is a single enantiomer or a racemic mixture thereof;

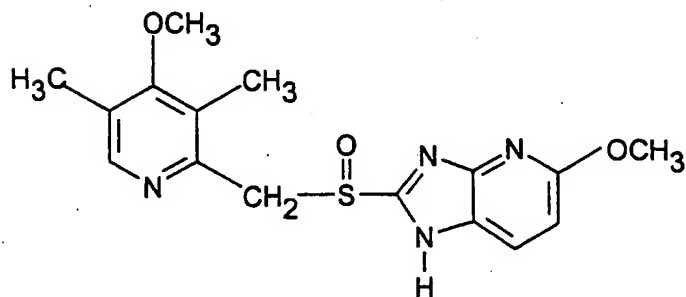
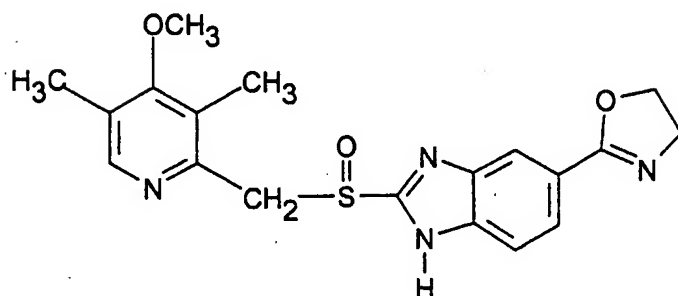
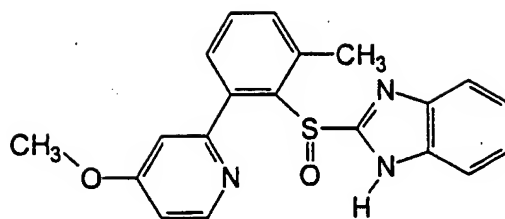
wherein each alkyl or alkylene moiety has a branched or straight chain and has 1 to 6,  
15 preferably 1 to 4, carbon atoms;

wherein a halogen atom is preferably a fluorine, chlorine, or bromine atom, preferably a fluorine or chlorine atom.

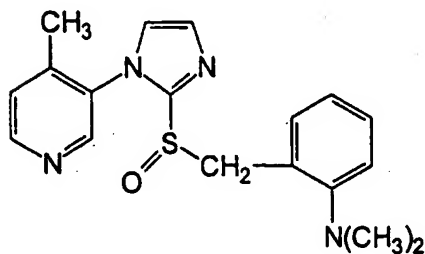
- 20 Examples of particularly preferred compounds according to formula I for use in the invention are







5 and



The  $H^+$ ,  $K^+$ -ATPase inhibitor used in the invention is preferably of formula (Ia): in other words it is preferably omeprazole, or an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole or an alkaline salt thereof.



The compound of formula (I) when optionally in the form of a pharmaceutically acceptable alkaline salt is preferably the  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Na^{+}$  or  $K^{+}$  salt, more preferably the  $Mg^{2+}$  salt.

The  $H^{+}$ ,  $K^{+}$ -ATPase inhibitor used in the invention can be administered orally, rectally or parenterally. While the effect of the inhibitors on the nasal polyps has been established in patients who have taken omeprazole by the oral route, it is believed that the effect of the inhibitor on the polyps is a systemic effect that is not dependent on what mode of administration is used. Accordingly a reduction in size of the polyps should be obtainable with other routes of administration.

Commercially available pharmaceutical preparations of  $H^{+}$ ,  $K^{+}$ -ATPase inhibitors are suitably used in the invention. Examples of such preparations for omeprazole include enteric coated pellets of omeprazole filled in capsules, or formulated into a multiple unit tableted dosage form; enteric coated tablets of omeprazole or an alkaline salt thereof; and solutions for parenteral administration comprising an alkaline salt of omeprazole.

The dose of the  $H^{+}$ ,  $K^{+}$ -ATPase inhibitor to be administered will vary according to the type of nasal polyps to be treated and the condition of the patient. However the dosage for oral, rectal or i.v. administration is generally in the range of from 1 to 100 mg of  $H^{+}$ ,  $K^{+}$ -ATPase inhibitor per day. Normally an amount of from 10 to 40 mg per day is used for oral administration.

The invention may be applied in combination with other treatments known to ameliorate the other symptoms generally associated with nasal polyps, for example asthma. In other words, the invention can be applied in the treatment of Widal's Syndrome which consists of the conditions of nasal polyps, asthma and aspirin intolerance. The invention may also be applied in the treatment of other inflammatory diseases in the upper respiratory tract such as acute and chronic rhinosinusitis, allergic and non-allergic rhinitis, as well as in the lower respiratory tract such as asthma. Therefore according to the invention there is further

provided a method for treating Widal's Syndrome and other respiratory tract inflammatory diseases which method comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome or the diseases a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid. According to the invention  
5 there is also provided a pharmaceutical formulation for simultaneous, separate or sequential administration to be used in the treatment of Widal's Syndrome or in the treatment of asthma which formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid. The invention further provides the use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of such a pharmaceutical formulation.

10 Preferred glucocorticoids are topically active anti-inflammatory steroids. Examples of suitable steroids include budesonide; rofleponide; rofleponide palmitate; ciclesonide; mometasone furoate; fluticasone propionate;  $16\alpha$ ,  $17\alpha$ -butylenedioxy- $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ ,  $21$ -dihydroxypregna- $1$ ,  $4$ -diene- $3$ ,  $20$ -dione;  $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ ,  $17\alpha$ -  
15 dibutylenedioxy- $17\alpha$ -methylthio-androsta- $4$ -ene- $3$ -one; S-methyl- $16\alpha$ ,  $17\alpha$ -butylenedioxy- $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy- $3$ -oxo-androsta- $1$ ,  $4$ -diene  $17\beta$ -carbothioate; methyl  $9\alpha$ -chloro- $6\alpha$ -fluoro- $11\alpha$ -hydroxy- $16\alpha$ -methyl- $3$ -oxo- $17\alpha$ -propionyloxy-androsta- $1$ ,  $4$ -diene- $17\alpha$ -carboxylate;  $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl- $3$ -oxo- $17\alpha$ -propionyloxy-androsta- $1$ ,  $4$ -diene- $17\beta$ -carbothioic acid S-( $2$ -oxo-  
20 tetrahydro-furan- $3$ S-yl) ester; tipredane; fluocinolone acetonide; flunisolide; flumethasone; dexamethasone; betamethasone; beclomethasone dipropionate; deflazacort; cortivazol; or cortisol and/or hydrocortisol, optionally in their pure isomeric forms (where such forms exist) and in the forms of their pharmaceutically acceptable salts.

25 The steroids for use in the invention may be applied using conventional dosing rates, e.g.  $40$  to  $3000$   $\mu g$  per day. Administration may be by inhalation orally or intranasally. The steroids can optionally be adapted to be administered from a dry powder inhaler, a pressurised metered dose inhaler, or a nebuliser.

When the steroids are administered from a pressurised inhaler, they are preferably in micronised form. They are suspended or dissolved in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with other propellants and/or surfactants and/or other excipients, for example ethanol, surfactants, lubricants, anti-oxidants and stabilising agents.

When the steroids are administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The invention is described more in detail with reference to the following examples.

#### *Example 1*

A 53 year old woman who had had Widal's Syndrome for several years but who had refused surgical treatment of her polyps suffered mild upper abdominal pain and no improvement in the polyps after treatment by topical and systemic corticosteroids. However within two weeks of being prescribed 20 mg of omeprazole per day in addition to 100 µg of budesonide (Aqua preparation) per nostril/b.i.d. and 6 mg of deflazacort per day, she experienced a progressive improvement in her nasal respiratory problem. Eventually she recovered completely from the polyps.

#### *Examples 2 to 10*

Nine patients, each with the conditions shown in the following Table 1, were treated during a two week period. The treatment consisted of 20 mg of omeprazole, 100 µg of intranasal budesonide and 3 to 15 mg of oral deflazacort (deflazacort was used in such a small quantity to ensure the patients' compliance). The results are also shown in Table 1.

Table 1

Example No.	Condition	Result
2	Widal's Syndrome	Temporary benefit
3	Widal's Syndrome	Positive effect
4	Widal's Syndrome	Positive effect
5	Nasal Polyposis	Long term benefit
6	Nasal Polyposis	No benefit
7	Nasal Polyposis	Positive effect
8	Nasal Polyposis	Positive effect
9	Nasal Polyposis and aspirin intolerance	Positive effect
10	Nasal Polyposis and asthma	No benefit

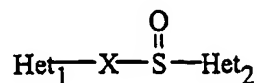
Where a positive effect is indicated, this means that the patient experienced a decrease in rhinorrhoea, a marked improvement in nasal respiratory ventilation and a reduction in the size of the polyps. The patient who experienced a temporary benefit by the treatment suffered a recurrence of the polyposis following the withdrawal of omeprazole and deflazacort (topical anti-inflammatory steroids, i.e. budesonide, were taken as required). However after treatment with the same regimen was resumed, a marked reduction in the size of the polyps was achieved.

10

The patient of Example 5 who experienced a long term benefit initially experienced no benefit at the end of the initial 2 week treatment period but continued with omeprazole and was rewarded with a positive effect at the end of 2 months.

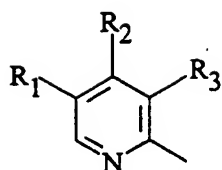
*Claims*

1. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor in the manufacture of a medicament for the treatment of nasal polyps.
2. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor in the manufacture of a medicament for the treatment of Widal's Syndrome.
3. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of a pharmaceutical formulation intended for simultaneous, separate or sequential administration in the treatment of Widal's Syndrome.
4. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of a pharmaceutical formulation intended for simultaneous, separate or sequential administration in the treatment of asthma.
5. Use according to claim 3 wherein the glucocorticoid is a topically active anti-inflammatory steroid.
6. Use according to claim 4 wherein the glucocorticoid is budesonide, beclomethasone dipropionate or fluticasone propionate.
7. Use according to any one of the preceding claims wherein the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound of formula

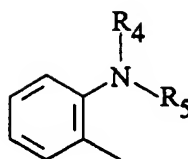
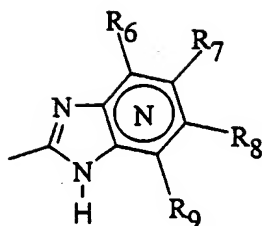


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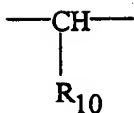
wherein  $\text{Het}_1$  is



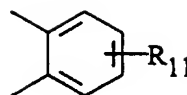
or

Het<sub>2</sub> is

5 and X is



or



wherein N in the benzimidazole moiety of Het<sub>2</sub> means that one of the ring carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub> and R<sub>3</sub> each independently represent hydrogen, alkyl, or alkoxy on the condition that R<sub>1</sub> and R<sub>3</sub> do not simultaneously represent alkoxy; and R<sub>2</sub> represents alkyl, alkoxy optionally substituted by fluorine, alkylthio or alkoxyalkoxy; or one of R<sub>1</sub> and R<sub>3</sub> is halogen and the other is hydrogen and R<sub>2</sub> is 1-morpholino, 1-piperidino or dialkylamino;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen and alkyl;

$R_6$ - $R_9$  are the same or different and selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy, alkylcarbonyl, and alkoxycarbonyl;

$R_{10}$  is hydrogen or  $R_{10}$  and  $R_3$  together complete a ring containing 6 to 8 carbon atoms;

5 and

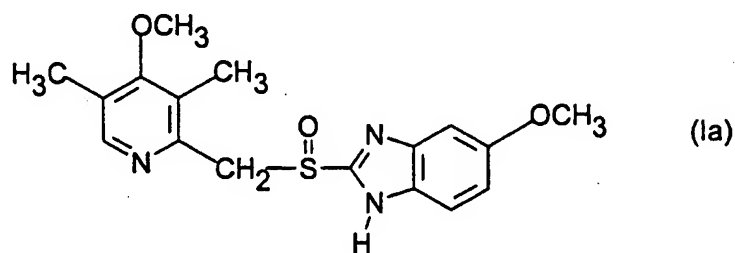
$R_{11}$  represents hydrogen, halogen or alkyl;

wherein the compound of formula (I) is optionally in the form of a pharmaceutically acceptable alkaline salt or in its neutral form or is a single enantiomer or a racemic mixture thereof;

wherein each alkyl or alkylenyl moiety has a branched or straight chain and has 1 to 6 carbon atoms.

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8. Use according to claim 7 wherein the compound of formula (I) is a compound of formula



20 or an alkaline salt thereof, or the (-)-enantiomer or an alkaline salt of the (-)-enantiomer.

9. A method for the treatment of nasal polyps which method comprises treating a subject suffering from the said condition with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor.

25

10. A method for the treatment of Widal's Syndrome which comprises treating a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor.
- 5 11. A method for the treatment of Widal's Syndrome which comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
- 10 12. A method for the treatment of asthma which comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
13. A method according to claim 11 wherein the glucocorticoid is a glucocorticoid defined in claim 5 or 6.
- 15 14. A method according to any one of claims 9 to 13 wherein the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound of the formula defined in claim 7 or 8.
- 20 15. A pharmaceutical formulation for simultaneous, separate or sequential use in the treatment of Widal's Syndrome which formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
- 25 16. A pharmaceutical formulation for simultaneous, separate or sequential administration in the treatment of asthma which pharmaceutical formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
17. A pharmaceutical formulation according to claim 15 or 16 wherein the glucocorticoid is a glucocorticoid defined in claim 5 or 6.



18. A pharmaceutical formulation according to any of claims 15 - 17 wherein the  $H^+$ ,  $K^+$  - ATPase inhibitor is a compound of the formula defined in claim 7 or 8.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/44, A61K 31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J CLIN GASTROENTEROL., Volume 23, No 1, 1996, M.M. YOUSFI et al, "Resolution of a Metaplastic Duodenal Polyp After Cure of Helicobacter pylori Infection" page 53 - page 54  --	1-2,7-8
A	American Journal of Gastroenterology, Volume 91, No 10, 1996, David Johnson, "World literature review" page 2245 - page 2246  --	3-8,15-18
A	US 4199578 A (NEIL A. STEVENSON), 22 April 1980 (22.04.80)  --	3-8,15-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 February 1998

Date of mailing of the international search report

27 -02- 1998

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4364923 A (PETER B. COOK ET AL), 21 December 1982 (21.12.82)  -- -----	3-8, 15-18

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-14  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
A method for treatment of the human or animal body by therapy, see rule 39.1
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept.

Invention 1. Claims 1 directed to the use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor for the manufacture of a medicament for the treatment of nasal polyps.

Invention 2. Claims 2 directed to the use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor for the manufacture of a medicament for the treatment of Widal's Syndrome.

Invention 3. Claims 3-8 and 15-18 directed to a system for simultaneous, separate or sequential use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor and a glucocorticoid, pharmaceutical compositions and the use thereof in the manufacture of a pharmaceutical formulation.

The special technical features of inventions 1 and 2 are new medical indications of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor. The special technical feature of invention 3 is a pharmaceutical composition comprising two different therapeutically active components which means an absolute product protection irrespective of the use.

Inventions 1 and 2 have been searched together.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.

PCT/SE 97/01651

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4199578 A	22/04/80	AU 525470 B	11/11/82
		AU 4210078 A	07/06/79
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